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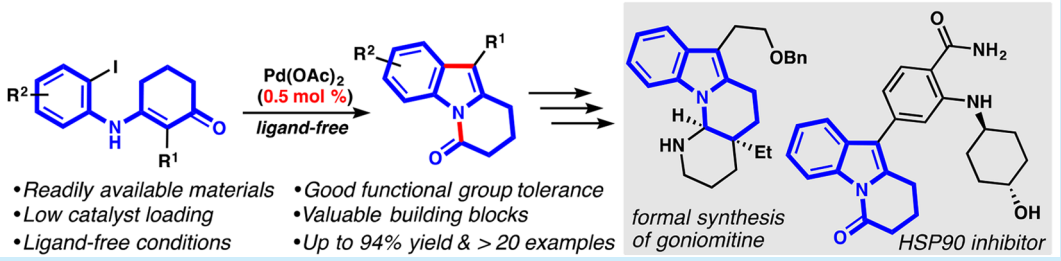
# Synthesis of *N*-Fused Polycyclic Indoles via Ligand-Free Palladium-Catalyzed Annulation/Acyl Migration Reaction

Zhan Dong,[†] Xiao-Wen Zhang,[†] Weishuang Li, Zi-Meng Li, Wen-Yan Wang, Yan Zhang, Wei Liu, and Wen-Bo Liu*

Engineering Research Center of Organosilicon Compounds & Materials, Ministry of Education, College of Chemistry and Molecular Sciences, Wuhan University, 299 Bayi Road, Wuhan, Hubei 430072, China

Supporting Information






**ABSTRACT:** An efficient synthesis of *N*-fused polycyclic indoles by a palladium-catalyzed annulation/acyl migration cascade reaction is described. The reaction is ligand-free, scalable, and provides access to a diverse range of useful indole scaffolds from readily available starting materials. Supporting mechanistic studies indicate that the reaction likely proceeds via an intramolecular $\alpha$-arylation mechanism. The synthetic utility of this protocol is demonstrated by a gram-scale reaction and syntheses toward indole alkaloids and a HSP90 inhibitor.

Heterocycles are present as core architectures in numerous bioactive molecules, both natural and synthetic. Among them, indoles have been recognized as privileged scaffolds for library design in drug discovery.[1] In particular, *N*-fused polycyclic indoles (i.e., dihydropyrido[1,2-*a*]indolones, DHPIs) are key skeletons[2] and crucial synthetic intermediates[3] of biologically important compounds (Figure 1). The

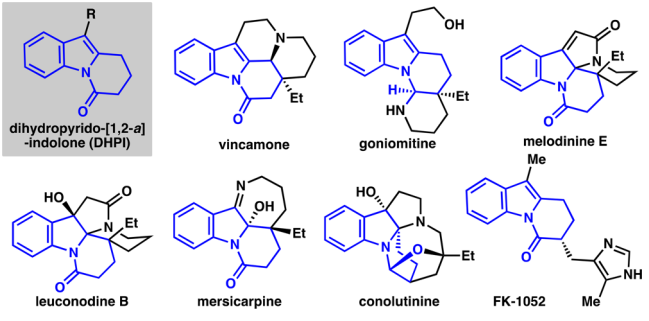



**Figure 1.** Representative natural products and pharmaceuticals containing DHPIs.

prominence of DHPIs was highlighted recently in the total synthesis of indole alkaloids.[3a−c] Although considerable progress has been achieved in the preparation of indole derivatives,[4−7] the direct and practical synthesis of *N*-fused polycyclic indoles remains a significant challenge.

To date, only a handful of examples of *N*-fused indole syntheses have been reported. A seminal report by Teuber et al.[7b] employing the classical Fischer indolization of monophenylhydrazines and $\alpha$-substituted-1,3-dicarbonyls provided the desired scaffold efficiently under acid conditions.[7] Palladium-catalyzed reactions (i.e., enamine coupling,[6f,k] tandem C−N/C−C coupling,[6r] and intramolecular heteroannulation[6c,d]) provided versatile entries into indole derivatives. An elegant report by Edmondson et al. delivered DHPI from 1,2-dibromobenzene and vinylogous amide using $Pd_2(dba)_3$/Davephos as catalyst, albeit with only one substrate.[6e] Rhodium-catalyzed electrocyclization/acyl migration of styryl azides and one-pot cyclization of alkyne-tethered phenylhydrazine/acid-promoted amide formation were also uncovered recently.[6g,h] It is rare but more desirable to develop a protocol with significantly reduced precious metal loading under ligand-free conditions. Inspired by the fact that the carbonyl group migrates preferentially over aryl and alkyl groups in indolenines **2**[6k,7b] and the Edmondson's precedent,[6e] we sought to develop a more efficient and straightforward route to DHPIs **3** by palladium-catalyzed cyclization of readily accessed enaminones **1** to form **2** followed by acyl migration (Scheme 1). Herein, we report the results of this synthetic approach with as low as 0.5 mol % of $Pd(OAc)_2$ alone as the catalyst.

We began our studies with enaminone **1a**, prepared from the condensation of 2-iodoaniline and 1,3-diketone in 88% yield,[8] as a model substrate. A brief screen of palladium sources was

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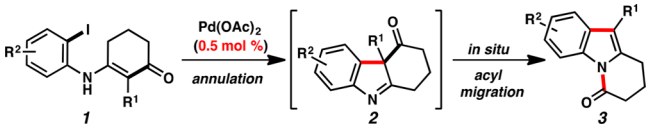
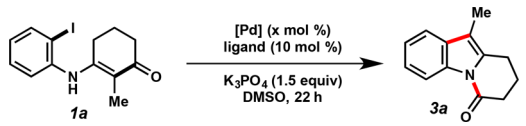
**Scheme 1. Synthesis of DHPIs by Palladium-Catalyzed Annulation/Acyl Migration Reaction**




initially conducted (see Table S1 in the SI). We were pleased to find that $Pd(OAc)_2$ alone[9] delivered the desired product **3a** in 74% yield (entry 1, Table 1). The use of $Pd(PPh_3)_4$ or

**Table 1. Optimization of the Reaction Conditions**



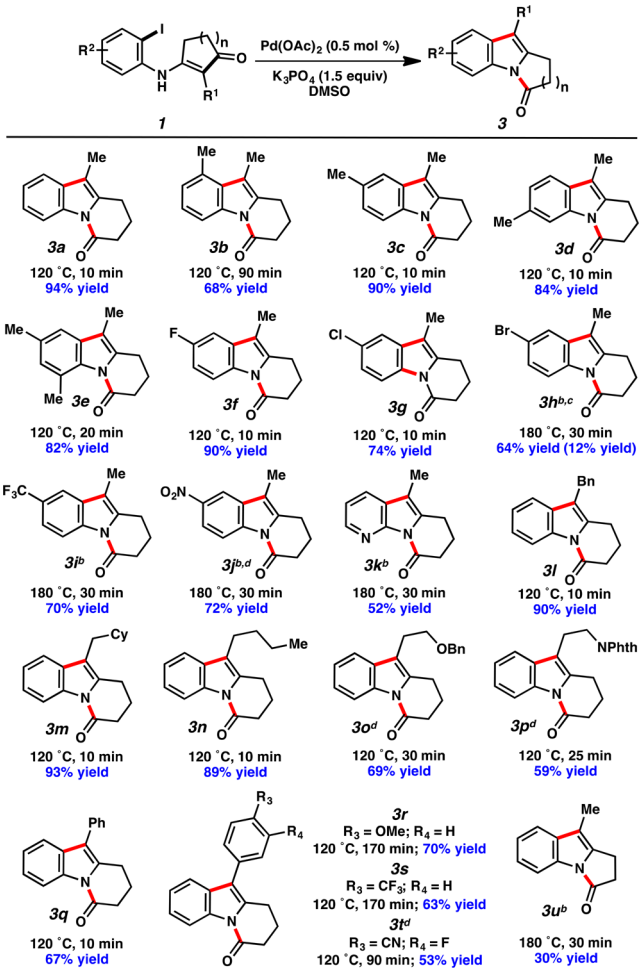

| entry[a] | [Pd] (*x*, mol %) | ligand | temp (°C) | yield[b] (%) |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (5) | *c* | 80 | 74 |
| 2 | $Pd(PPh_3)_4$ (5) | *c* | 80 | 54 |
| 3 | $Pd(OAc)_2$ (5) | P(*o*-tol)$_3$ | 80 | 78 |
| 4 | $Pd_2(dba)_3$ (2.5) | P(*o*-tol)$_3$ | 80 | 59 |
| 5 | $Pd(OAc)_2$ (1) | *c* | 80 | 77 |
| 6 | $Pd(OAc)_2$ (0.5) | *c* | 80 | 80 |
| 7 | $Pd(OAc)_2$ (0.2) | *c* | 80 | 36 |
| 8[d] | $Pd(OAc)_2$ (0.5) | *c* | 100 | 93 |
| 9[e] | $Pd(OAc)_2$ (0.5) | *c* | 120 | 94 |
| 10[f] | none | *c* | 120 | NR |

[a]Reactions conducted with 0.2 mmol of **1a** and 0.3 mmol of $K_3PO_4$ in 1 mL of DMSO. [b]Yield of isolated product. [c]Without the use of ligand. [d]For 30 min. [e]For 10 min. [f]For 1 h. NR, no reaction. For additional optimizations, see Tables S1–S4.

complexes derived from palladium precursors and P(*o*-tol)$_3$ resulted in 54–78% yield (entries 2–4). Reducing the loading of $Pd(OAc)_2$ obtained essentially the same yield (entries 5 and 6), while further reducing $Pd(OAc)_2$ to 0.2 mol % resulted in a diminished yield (entry 7). The reaction temperature was found to affect the reactivity dramatically, and 93% yield was obtained at 100 °C (entry 8). Although extensive investigation of reaction parameters was carried out for palladium with additional phosphine ligands (Tables S2 and S3), ligand-free system was found to be superior in terms of yield and catalyst cost (Table S4). Ultimately, treatment of **1a** with 0.5 mol % of $Pd(OAc)_2$ in DMSO at 120 °C (entry 9) was identified as the optimal condition.

With optimized condition in hand, the substrate scope of the reaction was then investigated (Scheme 2). We were delighted to find that an array of substituents on the aryl moiety, including Me, F, Cl, Br, $CF_3$, and $NO_2$, were well tolerated. Methyl substituents at the 4- and 5-positions of the anilines had limited effects on the outcome of the reaction (**3c**,**d**), but sterically encumbered 3-methyl substrate **1b** gave a lower yield to the corresponding 4-methylindole **3b** (68% yield), presumably due to the reduced rate of oxidative addition step. With electron-deficient substrates (i.e., Br, $CF_3$, and $NO_2$),[10] we found that applying microwave irradiation was crucial to accelerate the reaction, and the corresponding products were obtained in 64–72% yield (**3h–j**). It is noteworthy that an aryl bromide is amenable to this protocol and furnished product **3h** in 64% yield, accompanied by 12% of debrominated product (**3a**). Notably, 7-azaindole **3k** was

**Scheme 2. Substrate Scope[a]**




[a]Reactions performed under the conditions of entry 9, Table 1. [b]Under microwave irradiation. [c]Yield in the parentheses is the debromination product **3a**. [d]With 1 mol % of $Pd(OAc)_2$.

also synthesized in 52% yield, indicating the tolerance for additional heterocyclic functionality.

The effects of substituents on the enaminone moiety toward the reactivity were also examined. Substrates bearing alkyl chains of varying steric bulk and chain length (benzyl, cyclohexylmethyl, and *n*-butyl) were well compatible, providing **3l–n** in 89–93% yield. Importantly, benzoxyethyl- and phthalimide-containing dihydropyrido[1,2-*a*]indolones **3o** and **3p**, key precursors in *Aspidosperma* alkaloids synthesis, were furnished in 69% and 59% yield, respectively. Aside from aliphatic substituents, *α*-aryl-substituted enaminones were also studied and afforded 3-arylindoles **3q–t** in 53–70% yield. Finally, pyrrolo[1,2-*a*]indole **3u**, present in biologically active substances and drugs,[11] was also accessible from a five-membered enaminone albeit in low yield.

The intramolecular enaminone couplings were suggested to operate through two possibilities according previous studies, namely, *α*-arylation[6k,r] and Heck-type olefination.[5c] Likewise, mechanisms of our ligand-free reaction[12,13] were proposed as illustrated in Scheme 3a. Oxidative addition of substrate **1a** with a palladium(0) species, generated in situ from $Pd(OAc)_2$,[12−14] provides intermediate **I**. Olefin coordination forms complex **II**, which can subsequently undergo an *α*-arylation pathway (path a) or a Heck-type pathway (path b).



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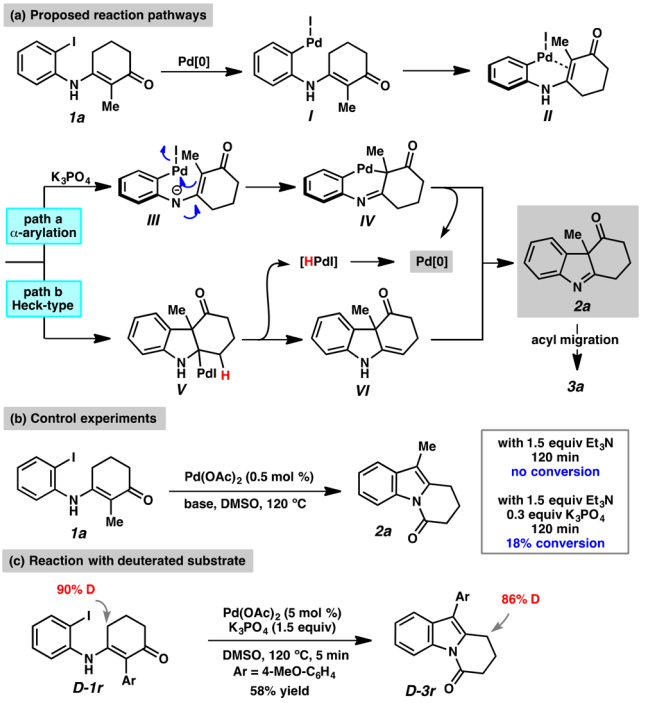
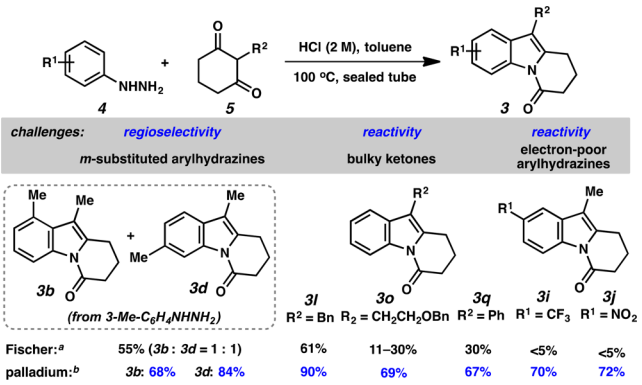
**Scheme 3. Proposed Reaction Pathways**




In path a, deprotonation of the enaminone **II** facilitates a nucleophilic attack onto palladium to generate six-membered metallacycle **IV**. Then reductive elimination of **IV** provides indolenine **2a** while regenerating the catalytically active species. In contrast, path b would proceed via a Heck-type mechanism: 1,2-olefin insertion followed by $\beta$-hydride elimination provides enamine **VI**. Tautomerization to **2a** and subsequent acyl migration again provide product **3a**. A similar acyl migration step (**2a** to **3a**)[15] has been previously observed by the Ban group[3e] in the Fischer indole process as well as by Edmondson et al. in the palladium catalysis.[6e] We then performed several experiments in order to gain insight into which pathway is operative under our conditions. In path a, a base capable of generating a nucleophilic, anionic species **III** is required. Studies probing the role of base emphasized the importance of $K_3PO_4$: weaker bases such as $Et_3N$ exhibited a complete lack of reactivity, whereas substoichiometric $K_3PO_4$ resulted in drastically reduced yield (Scheme 3b). Further experiments with deuterium-labeled substrate ***D*-1r** were carried out, and less than 4% isotope scrambling was observed (Scheme 3c). The minimal H/D scrambling of the $\gamma$-position of product ***D*-3r** indicates that the $\beta$-hydride elimination is less likely involved. While we could not rule out the possibility that abstraction of the proton on nitrogen of **V** forms palladium hydride species and product **2a**, the strained geometry of 5-*endo-dig* cyclization of the Heck pathway (from **II** to **V**) usually requires high energy thus is generally disfavored in palladium chemistry.[6r] Together, these results are in line with previous observations and support the $\alpha$-arylation pathway.[6k,r]

Next, the efficiency of this approach was evaluated by comparison with Fischer indolization protocols (Scheme 4).[4,7] Several DHPIs were prepared following known Fischer procedures with arylhydrazines **4** and 1,3-diketones **5**.[7] The application of *meta*-substituted arylhydrazines commonly exhibits poor regioselectivity in the Fischer indole process. Indeed, the use of *m*-tolylhydrazine afforded a 1:1 mixture of 4-

**Scheme 4. Comparison of Fischer Indole Synthesis with Our Method**




[a]Isolated yield of Fischer indolization; see the SI for conditions. [b]Yield of palladium-catalyzed reactions as shown in Scheme 2.

methylindole **3b** and 6-methylindole **3d**, isolated in 55% overall yield. We were pleased to find that the corresponding indoles (**3b** and **3d**) were synthesized in 68% and 84% yield, respectively, using palladium catalysis. With regard to either bulkier group substituted diketones ($R^2$ = Bn, $CH_2CH_2OBn$, and Ph) or electron-poor arylhydrazines ($R^1$ = $CF_3$ and $NO_2$),[16] the Fischer indolization resulted in lower yields (**3l**, **3o**, and **3q**) or no product formation (**3i** and **3j**). In particular, since the low efficiency of Fischer indolization toward **3o** synthesis (11−33%),[7a] an alternative route was then established enabling the total synthesis of monoterpene indole alkaloids practically albeit in multiple steps.[3a,b]

We have applied this method to the syntheses of indole alkaloids and bioactive compounds bearing distinct DHPI cores (Scheme 5). A gram-scale reaction with substrate **1o** was carried out with 1 mol % of $Pd(OAc)_2$ as catalyst and furnished DHPI **3o** in 74% yield. Notably, Li et al. also developed an efficient synthesis of **3o** with rhodium catalyst and finished the formal synthesis of goniomitine.[6g,17] Here, we offered a complementary synthetic route to aminal **7** including double alkylation of **3o** and a one-pot anti-Markovnikov hydroamination[18]/reductive cyclization of **6**.[3a,19] More generally, this method provides access to versatile synthetic intermediates that have previously been utilized in alkaloid synthesis. Hydrazinolysis of phthalimide **3p** afforded tryptamine **8** in 84% yield. Protection of the primary amine with methyl chloroformate furnished indole **9**, a synthetic intermediate en route to conolutinine by the Xie group,[20] in 69% yield. Importantly, tryptamine **8** can also be advanced to 9-membered lactam **10** under UV irradiation,[3d,e] which was previously employed in the total synthesis of a series of alkaloids in *Strychnos*, *Aspidosperma*, and *Schizozygane* families. Additionally, the HSP90 inhibitor **12**[21] was obtained in 53% overall yield from **3t** by a nucleophilic aromatic substitution and conversion of the nitrile to amide. Finally, *N*-fused indole **3a** itself was used as a key intermediate for the synthesis of FK-1052, which is a potent serotonin 3 and 4 (5-$HT_3$ and 5-$HT_4$) dual-receptor antagonist.[2]

In conclusion, an efficient synthesis of *N*-fused polycyclic indoles was realized by a palladium-catalyzed intramolecular annulation/acyl migration of enaminones. This expedient strategy features readily available starting materials, good compatibility with diverse functional groups, and low catalyst loadings and does not require expensive phosphine ligands. We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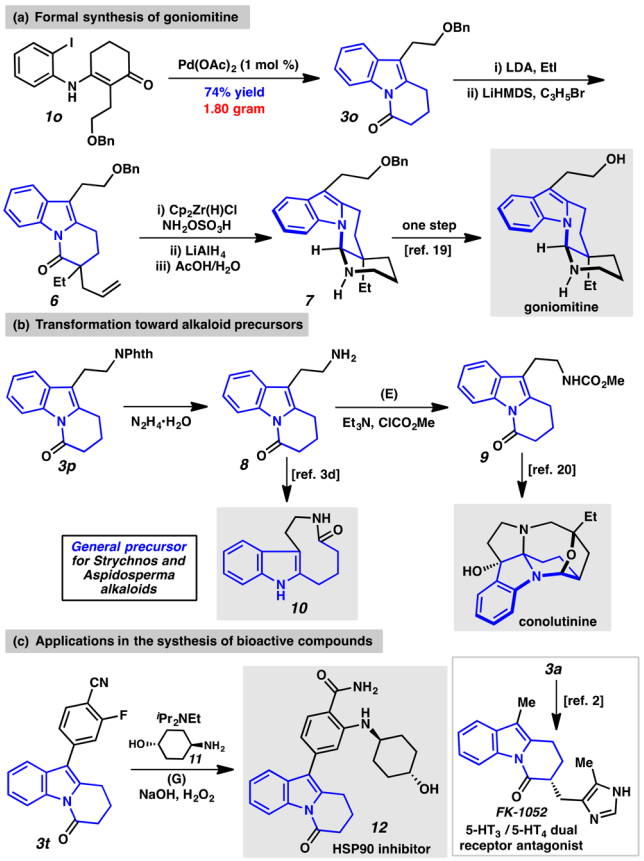
**Scheme 5. Synthetic Applications**[a]




[a]Conditions: (A) $Pd(OAc)_2$ (1 mol %), $K_3PO_4$, 4 Å MS, DMSO; (B) (i) LDA, THF, then EtI; (ii) LiHMDS, THF, then allyl bromide; 52% yield of two steps; (C) one pot: (i) $Cp_2Zr(H)Cl$, $NH_2OSO_3H$, THF; (ii) $LiAlH_4$, THF; (iii) $AcOH/H_2O$; 32% overall yield; (D) $N_2H_4 \cdot H_2O$, EtOH, 84% yield; (E) $Et_3N$, $ClCO_2Me$, $CH_2Cl_2$, 69% yield; (F) $^iPr_2NEt$, DMSO, 71% yield; (G) NaOH, $H_2O_2$, dioxane, 74% yield.

anticipate that the wide scope and efficiency of this new method will find broad utility across the synthetic community. Further applications in natural product synthesis are currently under investigation in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04128.

Detailed reaction condition optimizations, complete experimental procedures, characterization, and spectra for all new compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: wenboliu@whu.edu.cn.

### ORCID

Wen-Bo Liu: 0000-0003-2687-557X

### Author Contributions

†Z.D. and X.-W.Z. contributed equally.


### Notes

The authors declare no competing financial interest.

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(8) See the Supporting Information for details.

(9) Hydrolysis of **3a** to acid was observed following prolonged exposure to reaction conditions or with wet DMSO as solvent.

(10) Attempts to synthesize of enaminone subsrates by the condensation of electron-rich anilines (i.e., 4-methoxy-2-iodoaniline) with diketones were failed.

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